Regulatory Overview of Adequate and Well-Controlled Studies in TB Regimen Development

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Outline

- Regulatory requirements
  - Substantial evidence
  - Accelerated approval
  - Added contribution of components of TB regimen
- Design of Clinical Trial
  - Regimen vs. individual drug
  - Patient population
  - Control
  - Endpoints
  - Statistical analysis

Substantial Evidence of Effectiveness

- Required by law since 1962
  - Section 314.126 of Title 21 of the Code of Federal Regulations (CFR)
  - Adequate and well-controlled trials (interpreted as 2+)
- Clinical Effectiveness Guidance (1998)*
  - Gives situations were one adequate and well-controlled trial sufficient, along with independent substantiation of findings
  - For TB, possibly one adequate and well controlled trial plus information from Early Bactericidal Activity (EBA) studies and animal/in vitro studies
- Importance of adequate comparative safety data (at intended dose and duration)
  - Limited use indication (for patients without any options), safety database may be smaller

* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf

Accelerated Approval Program*

- Allows for earlier approval of drugs that treat serious conditions that provide meaningful therapeutic benefit over existing therapies
  - Uses an accelerated approval endpoint that is reasonably likely to predict clinical benefit, but is not itself a measure of clinical benefit
  - Can considerably shorten the time required prior to receiving FDA approval
- Required to conduct post-marketing studies to confirm the anticipated clinical benefit
  - If the clinical benefit is shown, then the FDA grants traditional approval for the drug.
  - If the clinical benefit is not shown, drug can be removed from the market.

*21 CFR 314 Subpart H

Standard vs. Accelerated approval

- If need for more complete information, more likely <u>standard approval</u>
  - Drug sensitive regimen – may need information on final long-term outcome before switching from highly effective (HRZE) treatment
- High impact regimen, more likely <u>accelerated</u>
  - MDR regimen – more effective, shorter duration, less toxic
    - if test regimen has markedly shorter duration, likely will need an endpoint that is past the end of treatment to make sure patients not at risk for very high relapse rate
  - XDR regimen

Accelerated approval of Bedaquiline*

- Approved in 2012 for the treatment of adults with MDR pulmonary tuberculosis

- Add-on trial: Randomized to Bedaquiline vs. placebo (24 weeks), all patients received best available therapy for 18-24 months

  – Accelerated approval was based on time to sputum culture conversion

  – Due to limited safety, "Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided"

- Confirmatory trial assessing long-term outcomes of failure, relapse or death at least 6 months after patients have completed TB treatment

* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf

Development of New TB regimens

- New regimen
  - Fixed-dose combination
  - Co-packaged product
  - Individually packaged, but labeled to be used in combination
- Efficacy and safety requirements similar for the three situations above

Combination Rule

- 21 CFR 300.50: Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects

  – Factorial design trial

    • 2 component regimen need at least a three-arm trial of AB, A, B

      – AB > A, demonstrates contribution of B

      – AB > B, demonstrates contribution of A

Added contribution

- 2013 Guidance on Codevelopment of Two or More New Investigational Drugs for Use in Combination*

  – Factorial designed clinical study is preferred

  – If not possible, then in vitro, in vivo animal models, phase 1, other early studies, with clinical study assessing the full regimen

* https://www.fda.gov/downloads/drugs/guidances/ucm236669.pdf

Designing a TB efficacy clinical trial

- Issues to consider are:
    - TB regimen vs. individual TB drug
    - patient population
    - control
    - endpoint
    - analysis

New regimen ⟷ New drug

- Totally New Regimen (high impact)
  - Examples:
    - 3-4 new drugs with new mech. of action to treat TB in 4-6 months
    - 2 new drugs with new mech. of action paired with an older drug
  - If contribution of effect of components from earlier phase of development, clinical trial may assess efficacy of regimen as a whole
- Single new TB drug being developed
  - Example:
    - A new drug to treat MDR given on top of a best available therapy
    - A new drug to replace one drug in the standard DS regimen
  - Efficacy of that single drug needed from clinical trial (Bedaquiline example)

Patient Population

- Drug Sensitive TB

- MDR-TB

- XDR-TB

- All combined

- Different patient populations
  - Possible different routes of approval (Accelerated vs. Standard)
  - Different controls

Control

- Expectation is for a randomized, controlled, blinded trial
  - If blinding is not feasible, trial should be conducted in a blinded manner as much as possible
- Control treatment depends on the patient population and regimen
  - For DS-TB that would be HRZE for 6 months
  - For MDR-TB, depends on the resistance patterns and location
- For XDR-TB, given poor outcome and long duration of treatment, may be possible for a drug with great effect to conduct a single arm trial with a historical control group

Control

- New single drug for MDR or XDR might use an add-on design
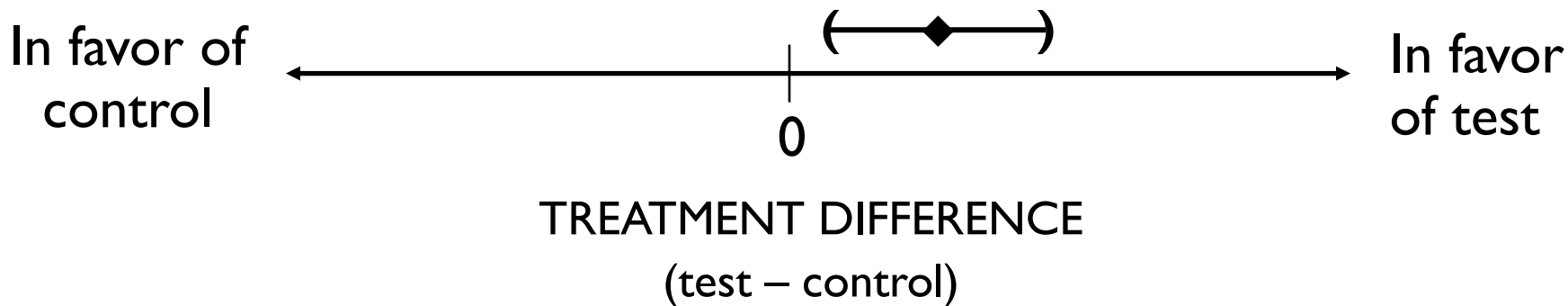
New drug + background regimen

vs.

Placebo + background regimen

Endpoints

- Early endpoints
  - Sputum culture conversion at 2 or 6 months
  - Time to sputum culture conversion
  - Note that these early endpoints do not test whether the planned duration of the regimen will be adequate
- Late endpoint
  - Sustained culture conversion measured approximately 6 – 12 months after treatment ends
  - Timing of endpoint based on time from randomization and is the same for the two treatment arms
  - Capture reason for failure: treatment failure, relapse, re-infection, lost to follow-up
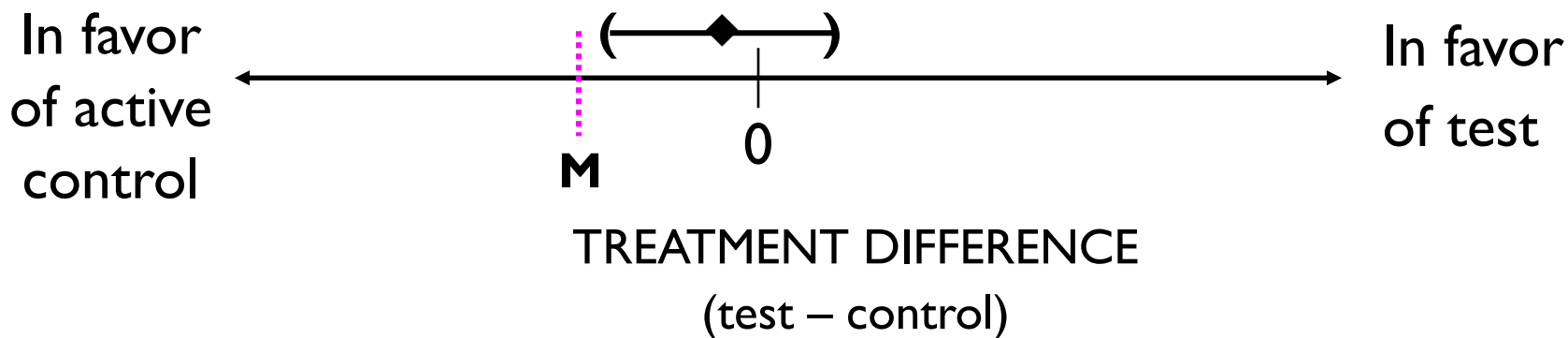
Analysis

- Superiority
  - Efficacy is determined by showing test arm is better than control
  - Typical for accelerated approval
  - Needed for add-on designs

In favor of control ←——————————|——(———◆———)——————————→ In favor of test

0

TREATMENT DIFFERENCE

(test – control)

Analysis

- Non-inferiority
  - Efficacy is determined by showing efficacy of test arm is "close to" a known effective control
  - How "close" it needs to be is the non-inferiority margin (M)
    - Depends on how effective the control is (based on data from previous trials) (**M1**)
    - How much efficacy willing to lose (clinical judgment) (**M2**)

In favor of active control ← (◆) → In favor of test

M   0

TREATMENT DIFFERENCE
(test – control)

Non-inferiority margin for TB

- Depends on specific trial design, including the patient population, timing and definition of endpoint.

- Assessing non-inferiority of a <u>test regimen</u> to the <u>control regimen</u>

  - Should be high impact regimen, NI assessment to make sure not losing anything on long-term endpoint

  - Control regimen as a whole has a large treatment effect compared to no treatment (M1 large)

    - In DS-TB, HRZE vs. no treatment,

    - In MDR-TB, best available therapy vs. no treatment

  - In this case, NI margin will be based largely on clinical judgment (M2)

Non-inferiority margin for TB

- Assessing non-inferiority of a <u>test drug</u> to a <u>control drug</u>
  - Control is a single drug in a multi-drug regimen
    - Its effect likely modest (M1 small)
    - Data likely limited to justify a margin
  - Examples:
    - New drug replaces ethambutol in the DS-TB regimen, HRZ**X** vs. HRZ**E**. The effect of **E** would need to be estimated (M1), to be sure that **X** has efficacy.
    - New drug added to DS-TB regimen and regimen is shortened by 2 months, 4HRZE**X** vs 6HRZE. The effect of the final 2 months of treatment would need to be estimated.
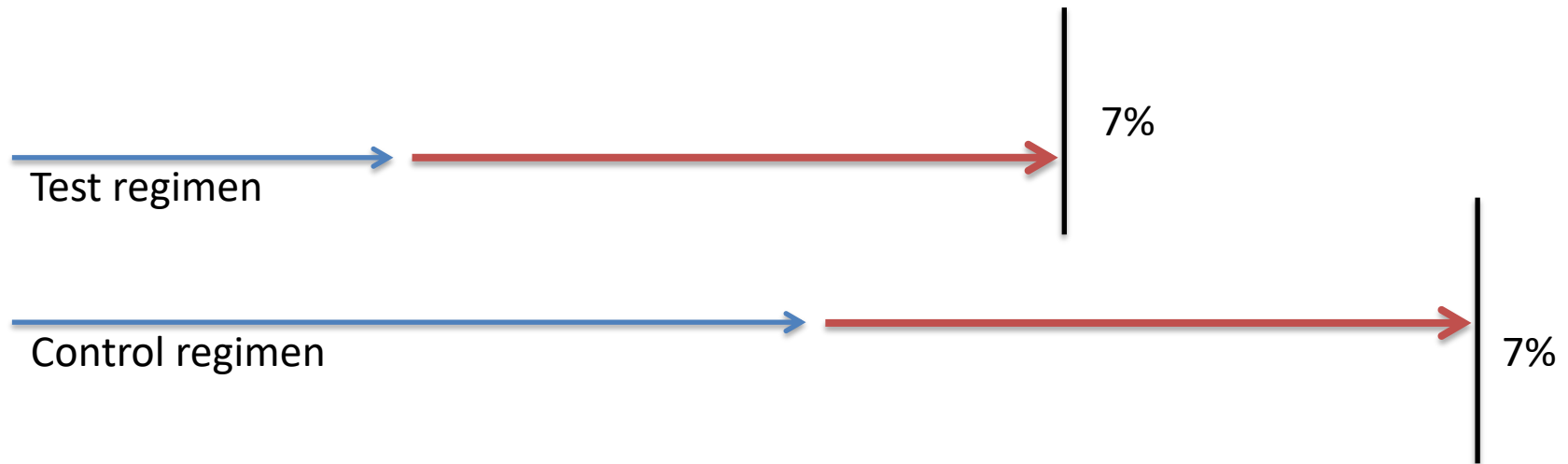
Conclusion

- Adequate and well controlled trial required to determine the efficacy of TB regimens or drugs
  - If developing a new regimen, need to put together evidence on contribution of each drug in the regimen
- Pathway of approval depends on the impact of the regimen
  - Accelerated approval is possible, might lead to limited indication, especially if safety data limited
- Development of a single drug will lead to different study design than development of a full regimen with high impact
- Important to discuss development program with FDA early

Thank you for all the work you are doing to further the treatment of tuberculosis

Timing of the endpoints

Test regimen   7%

Control regimen   7%

Test (4 month) and control (8 month) regimens appear the same comparing 6 month post treatment in terms of failure. But they are comparing different quantities, making it appear that a subject will do equally well on the two regimens.

Timing of the endpoints

Test regimen

Control regimen

15%

7%

Test (4 month) and control (8 month) regimens no longer appear the same in terms of failure when comparing both at a fixed time from randomization. Now it is clear that a patient has a higher likelihood of not doing well on the test regimen.